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(21) International Application Number: PCT/GB98/03732 (22) International Filing Date: 17 December 1998 (17.12.98) (30) Priority Data: 9727126.6 22 December 1997 (22.12.97) GB (71) Applicant (for all designated States except US): ZENECA LIMITED [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): PEARS, David, Alan [GB/GB]; Hexagon House, P.O. Box 42, Blackley, Manchester M9 8ZS (GB). DENTON, Bruce, John [GB/GB]; 17 Millersdale Grove, Runcorn, Cheshire WA7 2QH (GB). DENTON, Bruce, John [GB/GB]; 17 Millersdale Grove, Runcorn, Cheshire WA7 2QH (GB). (74) Agents: REVELL, Christopher; Zeneca Specialties, Intellectual Property Group, Hexagon House, P.O. Box 42, Blackley, Manchester M9 8ZS (GB) et al.		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PROCESS FOR THE PREPARATION OF SOLID POLYMER COMPOSITES (57) Abstract A process for the production of solid polymer composites, polymer composites obtainable by the process, the use of the polymer composites as solid supports for chemical synthesis, and chemical libraries synthesised on the polymer composites are described. The process comprises polymerising a non-(meth)acrylate monomer, oligomer or monomer/oligomer mixture, in a substantially planar inert porous non-cellulosic solid substrate under conditions whereby the non-(meth)acrylate monomer, oligomer or monomer/oligomer mixture is substantially unreactive towards the substrate. Preferably, the polymer composite produced comprises a functionalised polystyrene.		

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PROCESS FOR THE PREPARATION OF SOLID POLYMER COMPOSITES

The present invention relates to a process for the production of solid polymer composites, polymer composites obtainable by the process, the use of the polymer
5 composites as supports for chemical synthesis, and chemical libraries synthesised on the polymer composites.

The technique of combinatorial chemistry is an increasingly important tool for the rapid production of large numbers of chemically diverse molecules. In, for example, the pharmaceutical and agrochemical industries, chemical libraries produced by this
10 technique may be screened to identify new lead compounds having biological activity.

Chemical libraries may be produced by either solution phase or solid phase synthesis, *Angew. Chem. Int. Ed. Engl.*, 1996, **35**, 2288-2337, provides a review of combinatorial chemistry using these approaches.

The use of solid phase synthesis for the production of chemical libraries has the
15 advantage that it facilitates the physical separation of the compounds produced. In addition, solid supports may be labelled or tagged such that the identity or reaction history of a compound attached to a particular solid support can be elucidated.

Solid phase synthesis performed on discrete solid supports such as resin beads can generate very large numbers of compounds using a "split and mix" technique, as
20 described in *Int. J. Peptide Protein Res.*, 1991, **37**, 487-493. The beads used in this technique generally have a diameter of from 100 to 200 μm . However, handling beads of this size can be problematic and their size means that on average only about 10^{-11} to 10^{-8} mol of compound can be synthesised per bead which may not be a sufficient quantity for some screening operations.

25 EP 288310 discloses solid supports for use in chemical synthesis, chromatography and ion exchange techniques which comprise a porous polymeric material, having a shape and configuration resulting from the polymerisation of a precursor material in a high internal phase emulsion system, and a gel retained within the pores of the polymeric material. The gel is retained within the pores of the polymeric
30 material by chemical binding of the gel to the polymer surface and/or by swelling of the polymeric material.

WO 96/16078 discloses a method of synthesising chemical libraries on sheets of laminar solid support material. In this method the sheet of support material is divided into a number of discrete reaction zones and different compounds are synthesised within
35 each of the zones. Suitable laminar solid supports for use in this process are said to include polyethylene or polypropylene films grafted with polystyrene, such as those described in WO 90/02749. Alternatively, the laminar supports may be made by sandwiching a layer of particulate solid support resin, e.g. cross-linked polystyrene containing amino groups, between two layers of a porous inert material such as a

polypropylene sheet. The process for making these supports comprises mixing the particulate solid support resin with an adhesive, spreading this over the surface of a sheet of porous inert material, applying a second sheet of porous inert material, then heat welding the sandwich so as to trap the resin.

5 Good adhesion between the inert substrate and the polymer is vital for a synthetically useful composite; the polymer must not lift off the inert substrate during the repeated mechanical and solvent/chemical stresses it will face during chemical library synthesis.

10 We have now found that particularly advantageous polymer composites which are suitable for use as solid supports for the synthesis of chemical libraries can be made by forming an impregnate of a functionalised cross-linked polymer in an inert substrate material.

15 Therefore, according to the invention there is provided a process for the production of a functionalised cross-linked non-(meth)acrylate polymer composite comprising polymerising a non-(meth)acrylate monomer, oligomer or monomer/oligomer mixture, in a substantially planar inert porous non-cellulosic solid substrate under conditions whereby the non-(meth)acrylate monomer, oligomer or monomer/oligomer mixture is substantially unreactive towards the substrate.

20 The polymer composites produced by the process of the invention are novel. Therefore, according to a further aspect of the invention, there is provided a functionalised cross-linked polymer composite obtainable by a process comprising polymerising a non-(meth)acrylate monomer, oligomer or monomer/oligomer mixture, in a substantially planar inert porous non-cellulosic solid substrate under conditions whereby the non-(meth)acrylate monomer, oligomer or monomer/oligomer mixture is substantially unreactive towards the substrate.

25 The polymer composites produced according to the invention have various advantages over support materials known from the prior art for use in the synthesis of chemical libraries. In particular, they exhibit greater mechanical and chemical resilience, this advantage is a direct consequence of the *in situ* polymerisation in the inert substrate since it means that, even though the polymer and substrate are not chemically bound to each other, they cannot be separated without breaking chemical bonds within the polymer. Since the polymer composites are not limited in size, like conventional resin beads, they also allow greater quantities of compound to be synthesised. Furthermore, direct polymerisation in an inert substrate offers various manufacturing advantages over both laminar solid supports and grafted solid supports. Direct polymerisation also allows greater flexibility in the choice of both polymer and inert substrate. Laminar solid supports require polymer beads to be manufactured prior to adhesion to the substrate, such beads are conventionally made by suspension polymerisation which is a lengthy process to optimise for any particular polymer, and is limited to the use of monomers

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which are not reactive with the suspension phase, e.g. water. Grafting, such as radiation grafting, can also impose restrictions on the choice of polymer and substrate since they must not decompose during radiation. Furthermore, the substrate must be one which produces suitable radical sites for the polymer/monomer to graft on to.

5 Inert porous non-cellulosic solid substrates which may be used in the process of the invention may comprise any porous non-cellulosic material that is inert under a range of conditions commonly used in chemical library synthesis. Such materials will therefore be inert to a range of temperatures, solvents and chemical reagents. The porous solid substrate is preferably non-swelling in solvents such as those commonly used in
10 chemical synthesis. The porous solid substrates may have any physical form having an interstice size suitable to accommodate the polymer. The substrate is preferably microporous. Increased porosity increases the surface area available for polymerisation such that higher loadings of polymer in the substrate can be obtained. Examples of suitable physical forms for porous non-cellulosic solid substrates include webbing,
15 meshes, nets, felts, textiles/fabrics, sponges, membranes, woven mats, heatwelded mats and composite mats/felts. Examples of suitable materials include plastics such as PTFE, polyethylene or polypropylene e.g. Leutrasil VS3450 thermally bonded polypropylene Spunweb (Leutrasil is a trademark of Carl Freudenberg, FRG Weinheim. Spunweb describes a type of fabric made by an integrated process which converts granular raw
20 material directly into textile fabric); fabrics such as cotton, wool polyester or polyamide; metal and carbon fibre.

The substantially planar non-cellulosic solid substrate is preferably a flat sheet like material such that the polymer composite formed in the process of the invention has a structure that extends essentially in 2-dimensions. Once they have been formed, sheet
25 like composites may be cut into any shape and size suitable for their intended purpose. Substantially planar solid substrates may also be assembled into 3-dimensional shapes, e.g. tubes, either before or after impregnation of the cross-linked polymer.

Non-(meth)acrylate polymers which may be formed in the process of the invention include any cross-linked non-(meth)acrylate polymer which has appropriate functionality,
30 or may be functionalised, to render it suitable as a support for chemical synthesis. Hydrophobic or hydrophilic non-(meth)acrylate polymers employed can be formed in the process of the present invention. Examples of suitable hydrophobic polymers include those based on styrene and substituted styrenes, for example alkyl, halo, amino, hydroxy, acetoxo or carboxy styrenes such as chloromethylstyrene; 4-bromostyrene; and
35 styrenes and substituted styrenes modified with polyethylene glycol. In many preferred embodiments, the polymer composition will contain a polymerised multi-functional vinyl species, e.g. divinyl benzene, to act as a crosslinker. Examples of suitable hydrophilic polymers include those based on (meth)acrylamides, and those based on (meth)acrylamides together with styrene type monomers. Examples of suitable

(meth)acrylamide monomers are N-acryloyl sarcosine methyl ester, cross-linked with N,N'-bis-acryloyl ethylene diamine.

Preferably, the polymer produced is a hydrophobic polymer, and the most preferred cross-linked polymers comprise substituted styrenes.

5 The functionalised cross-linked polymer composites produced according to the process of the invention are functionalised so as to render them suitable for solid phase chemical synthesis. Functionalisation of the polymer allows the attachment of chemically reactive ligands to the polymer which can then be used in the synthesis of chemical libraries. The monomer, oligomer, or monomer/oligomer mixtures from which the cross-linked polymer is formed may be pre-functionalised, or the cross-linked polymer may be
10 post-functionalised after it is formed in the inert substrate. Pre-functionalisation is preferable to post-functionalisation since it allows higher levels of functionality to be introduced into the polymer and avoids the batch variation often exhibited in post-functionalised polymers. The ability to use pre-functionalised polymers gives the polymer
15 composites of the invention an advantage over grafted polymer composites which are not amenable to pre-functionalisation.

 The monomer, oligomer or monomer/oligomer mixture may be introduced into the inert substrate using any suitable method, for example, the substrate may be immersed in the monomer, oligomer or monomer/oligomer mixture, or it may be coated onto the
20 inert substrate using, for example, a wire draw bar. A uniform coating of the monomer, oligomer or monomer/oligomer mixture on the inert substrate is preferred, particularly when the substrate is a flat sheet like material. Other suitable methods for producing the polymer composites include 'hand lay up' which comprises applying the monomer, oligomer or monomer/oligomer mixture to the substrate then rolling it into the substrate to
25 obtain intimate contact between the polymer and substrate; and 'pultrusion' which comprises pulling the substrate through a bath of oligomer in which polymerisation has been initiated, then heating to complete polymerisation.

 The process of the invention preferably comprises initiating polymerisation in the monomer, oligomer, or monomer/oligomer mixture prior to its introduction onto the inert
30 substrate. Typically the monomer, oligomer, or monomer/oligomer mixture will be premixed and an initiator added to initiate polymerisation. The initiator used will obviously depend on the monomer, oligomer, or monomer/oligomer mixture, examples of initiators include free radical initiators such as 2,2'-azobisisobutyronitrile, 2,2'-azobis(2,4-dimethyl valeronitrile), dioctanoyl peroxide and *tert*-amyl peroxyneodecanoate. The
35 monomer, oligomer, or monomer/oligomer mixture may also be heated to assist polymerisation, the temperature to which it is heated will obviously depend on the particular monomer(s)/oligomer(s) and initiators, however suitable temperatures are in the range 15 to 160°C, for example 60°C.

Once polymerisation of the monomer, oligomer or monomer/oligomer mixture is initiated the viscosity of the polymerising mixture will rise with time. It has been found advantageous to coat the polymerising mixture onto the inert substrate whilst it is at a fairly low viscosity, i.e. at a low extent of polymerisation, so that most of the molecular weight build up occurs *in situ* in the inert substrate. If the polymerisation reaches too high a conversion prior to application the coating may be difficult to apply uniformly because of high viscosity and additionally it may have poor adhesion to the inert substrate. The low-shear viscosity of the polymerising mixture when applied to the inert substrate is often at least 1 mPas, and in many embodiments is no more than 200 Pas. Preferably, the low shear viscosity is in the range of from 1 Pas to 100 Pas, and particularly in the range of from 10 to 50 Pas.

In a preferred aspect the process comprises polymerising a non-(meth)acrylate oligomer or monomer/oligomer mixture, in a substantially planar inert porous non-cellulosic solid substrate under conditions whereby the non-(meth)acrylate oligomer or monomer/oligomer mixture is substantially unreactive towards the substrate. The oligomer or monomer/oligomer mixture may be referred to as a prepolymer. A prepolymer is a mixture that is capable of further polymerisation and comprises a low molecular weight polymer (oligomer) and, optionally, unreacted monomer units.

Completion of the polymerisation in the inert substrate may be achieved by heating the composite, e.g. in an oven, until the required degree of polymerisation is obtained; or by UV radiation curing. An alternative and preferable method is to mix into the monomer, oligomer or monomer/oligomer mixture immediately prior to its introduction into the inert substrate a low temperature free radical initiator, e.g. methyl ethyl keto peroxide, optionally in combination with a suitable accelerator, e.g. cobalt octoate, which will catalyse polymerisation at or near room temperature. Examples of other low temperature initiators include 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile), diisobutanoyl peroxide, cumyl peroxyneodecanoate, 2,4,4-trimethylpentyl-2-peroxyneodecanoate, *tert*-amyl peroxy neodecanoate. A combination of amine accelerators, such as N,N-dimethyl aniline or N,N-dimethyl p-toluidine, with low temperature reactive initiators may also be used.

Following polymerisation of the monomer, oligomer or monomer/oligomer mixture in the inert support the polymer composite is preferably washed with solvent to remove any monomer, low molecular weight polymer, initiator fragments and polymer which does not form part of the composite. Suitable solvents for the washing procedure include THF, alcohols such as methanol and ethanol, DMF, toluene, ethyl acetate, and ethers such as diethyl ether and butyl methyl ether, or mixtures thereof.

As mentioned previously the polymer composites of the invention find application as solid supports for the synthesis of chemical libraries. The polymer composites of the invention are of particular use in an adaptation of the process described in WO 96/16078

for the synthesis of chemical libraries. In this process, a sheet of the polymer composite is divided into a number of individual reaction zones within which compound synthesis is performed. Alternatively, the polymer composites may be cut into discrete pieces, e.g. square, rectangular, triangular or circular in shape, which are suitable for use in the synthesis of chemical libraries by a "split and mix" technique. Whichever process is used for the chemical library synthesis it will involve applying at least two different reagents to each area of the polymer composite comprising a discrete reaction zone.

Thus according to a further aspect of the invention there is provided the use of a polymer composite according to the invention as a solid support for chemical library synthesis.

There is also provided a chemical library comprising a plurality of different chemical compounds bound to discrete portions of a polymer composite according to the invention.

The chemical libraries according to this aspect of the invention will generally comprise at least 10 different compounds, and preferably contain at least 50 different compounds, for example between 10^2 and 10^{10} compounds.

Chemical libraries produced using the polymer composites of the invention as solid supports may comprise a wide variety of chemically diverse compounds. The polymer composites may be used for any type of solid phase synthesis which is conventionally performed on resin beads. The chemical libraries produced may comprise any compounds which can be synthesised using, for example, the stepwise addition of a number of building blocks and/or reagents. Examples of compounds which may be synthesised in this manner include peptides, oligonucleotides and synthetic small molecules.

The use of discrete pieces of the polymer composites in the synthesis of a chemical library by a "split and mix" technique is illustrated by the following protocol for the preparation of a 27-membered library starting from 3 sets of reagent building blocks to produce trimer compounds: 27 Discrete pieces of polymer composite are taken, divided into groups of 9, and placed into 3 separate reaction pools A, B and C. If a "directed sort" step is used during the synthesis it may be convenient to use different shapes for the composites in pools A, B and C. The 9 pieces in pool A are then reacted with reagent A1, the 9 pieces in pool B are reacted with reagent B1 and the 9 pieces in pool C are reacted with reagent C1. The 27 pieces are then subject to a "directed sort" or "pick and place" so that each of the pools A, B and C contains $3A1 + 3B1 + 3C1$. Pool A is then reacted with reagent A2 to produce $3A1A2 + 3B1A2 + 3C1A2$, pool B is reacted with reagent B2 to produce $3A1B2 + 3B1B2 + 3C1B2$, and pool C is reacted with reagent C2 to produce $3A1C2 + 3B1C2 + 3C1C2$. The 27 pieces in pools A, B and C are then subjected to a further "directed sort" or "pick and place" so that pools A, B and C each contain A1A2, B1A2, C1A2, A1B2, B1B2, C1B2, A1C2, B1C2 and C1C2. Pool A is then

reacted with reagent A3 to produce A1A2A3, B1A2A3, C1A2A3, A1B2A3, B1B2A3, C1B2A3, A1C2A3, B1C2A3 and C1C2A3, pool B is reacted with reagent B3 to produce A1A2B3, B1A2B3, C1A2B3, A1B2B3, B1B2B3, C1B2B3, A1C2B3, B1C2B3 and C1C2B3, and pool C is reacted with reagent C3 to produce A1A2C3, B1A2C3, C1A2C3, A1B2C3, B1B2C3, C1B2C3, A1C2C3, B1C2C3 and C1C2C3. The synthesis thus results in 27 discrete pieces of polymer composite each bearing a unique trimer compound. The trimer compounds are prepared in 3 reaction pools using 9 (3+3+3) reactions.

In a similar process it would be possible to make 1,000 compounds as trimers using 10 sets of reagents in 10 pools. So that 30 (10+10+10) reactions would give 1,000 (10x10x10) different compounds.

The polymer composites of the invention may be used in the synthesis of chemical libraries by either manual or automated techniques. When the chemical libraries are synthesised by automated techniques, strips of the polymer composites may advantageously be coiled into reaction tubes such that a robotic probe can aspirate liquid, e.g. a reaction mixture or wash solution, contained within the tube without touching the polymer composite.

Chemical compounds synthesised using the polymer composites of the invention as solid supports, will generally be attached to the functionalised cross-linked polymer by means of a linking group. The linking group will be provided with appropriate functionality to enable it to bind at one end to the functionalised cross-linked polymer and at the other end to the precursor of the compound to be synthesised. Cleavable linkers may be used to facilitate removal of the compounds from the polymer composite prior to screening and/or identification. Suitable linking groups include those present in, for example, trityl chloride resin, Rink amide resin, Wang resin and Kaiser oxime resin.

The polymer composites may be labelled or tagged prior to, or during, chemical synthesis, such that at least part of the reaction history of a particular piece of polymer composite or area of polymer composite can be elucidated. Information about the reaction history provided by the label or tag can be used to identify, in part or full, the structure of the compound synthesised on a particular piece or area of polymer composite. Labelling of the polymer composite may comprise marking with individual reaction zones on a sheet of the composite, for example as described in WO 96/16078, or marking discrete pieces of polymer composite. Suitable indica include visible indica such as numbers, letters, symbols or colours which may be printed onto the polymer composite prior to library synthesis, such indica may be 2- or 3-dimensional. Alternatively, polymer composites provided in discrete pieces may have unique shapes, e.g. formed by cutting into an edge of the composite, such that they can be identified e.g. by machine reading. Polymer composites may also be labelled with bar-codes e.g. as described in WO 97/12680 and WO 97/32892, chemical structures e.g. as described in WO 94/08051, or electromagnetic systems e.g. as described in WO 96/36436. When the

polymer composites are formed into 3-dimensional shapes, e.g. tubes, a tagging system such as a bar code or electromagnetic tag may be inserted into tube which is then sealed, e.g. as described in WO 97/12680 and WO 96/36436.

5 In a preferred aspect of the invention portions of a polymer composite comprising discrete reaction zones for chemical synthesis are labelled, such that at least part of the reaction history of an individual zone can be elucidated following said chemical synthesis.

As an alternative, or adjunct, to labelling, analytical methods such as mass spectrometry and/or nuclear magnetic resonance spectrometry may be used to identify compounds synthesised on a particular area of polymer composite.

10 Following library synthesis the compounds making up a chemical library may be cleaved from the polymer composite prior to screening for biological activity, or they may be screened *in situ* whilst still linked to the polymer composite. The screening method used will depend on the composition of the chemical library and the nature of the screen.

The invention is illustrated by the following none limiting examples:

15

Example 1

4mmol/g Chloro methyl styrene composite

20 Chloro methyl styrene (40/60 mixture of 3 and 4 isomers) (11.7 g), styrene (7.5 g), technical grade divinyl benzene (0.4 g) and AIBN (0.4 g) were mixed in a glass vessel and heated to 60°C. After 2 hours the heating was stopped and methyl ethyl peroxide (0.4 g) and cobalt octoate (2 drops) were mixed into the polymerisation and the material immediately coated onto a Leutrasil VS3450 mat using a wire coater bar. The polymerisation was allowed to continue to completion at room temperature. Once polymerisation was complete the coated mat was washed with THF to remove any
25 monomer, low molecular weight polymer, initiator fragments and polymer which was not part of the composite.

Example 2

100% Polystyrene composite

30 The procedure of Example 1 was repeated using styrene (19.2 g), technical grade divinyl benzene (0.4 g) and AIBN (0.4 g).

Example 3

Preparation of Poly(4'anisoyl)-4-styrene Polymer Composite

35 3 Sheets of the polystyrene composite of Example 2 (3.13 g, approximately 10 x 10 cm) were covered with dichloromethane (DCM) (36 ml) and shaken on an orbital shaker for 5 min. 4-Anisoylchloride (5.2 g) and iron (III) chloride were added and the reaction mixture shaken for 3 days. The composite was removed from the reaction solution and washed with DCM (x2), a mixture of 3:1 THF/1M aqueous HCl (x3), THF

(x2), DCM, THF, and finally methanol (MeOH), sufficient wash solution was used to cover the composite. The composite was dried in a vacuum oven at 50°C for 16 hours. The resultant composite (3.27 g) was a light brown colour.

5 Example 4

Preparation of Poly(4'-methoxyphenyl-hydroxymethyl)-4-styrene Polymer Composite

The pieces of composite (3.0 g) from Example 3 were cut into 4 and covered with THF (33 ml). Lithium borohydride (0.15 g) was added in two portions over 10 min and the reaction mixture stirred for 3 hours at ambient temperature then refluxed for 3 hours.
10 A further portion of lithium borohydride (0.15 g) was added and the mixture refluxed for 16 hours. The composite was removed from the cooled reaction mixture and washed with a mixture of 1:1 MeOH/THF (x2), 3:1 THF/water (x2), THF (x2) and finally MeOH (x2). The composite was dried in a vacuum oven at 50°C for 16 hours. The resultant composite (3.0 g) was a light buff colour.

15

Example 5

Preparation of Poly(4'-methoxyphenyl-chloromethyl)-4-styrene Polymer Composite

The pieces of composite from Example 4 were covered with a 25% solution of acetyl chloride in toluene (50 ml). The reaction mixture was heated to 65°C for 16 hours.
20 The composite was removed from the solution and washed with toluene (x3), DCM (x2), THF (x2) and finally ether. The composite was dried in a vacuum oven at 50°C for 16 hours. Microanalysis showed C = 82.0%, H = 9.92%, Cl = 5.53%.

Example 6

25 Preparation of Poly[4'-methoxyphenyl-(2-thiophenylmethylamino)methyl]-4-styrene Polymer Composite

The pieces of composite from Example 5 were covered with THF (50 ml) and 2-thiophene methylamine (4.9 ml) added, this reaction mixture was stood for 3 days. The composite was removed from the solution and washed with THF (x3), DCM (x2) and
30 finally MeOH (x2). The composite was dried in a vacuum oven at 50°C for 16 hours. The resultant composite (3.2 g) was a light brown colour. Microanalysis showed C = 83.77%, H = 10.06%, N = 0.92%, S = 2.83%.

Example 7

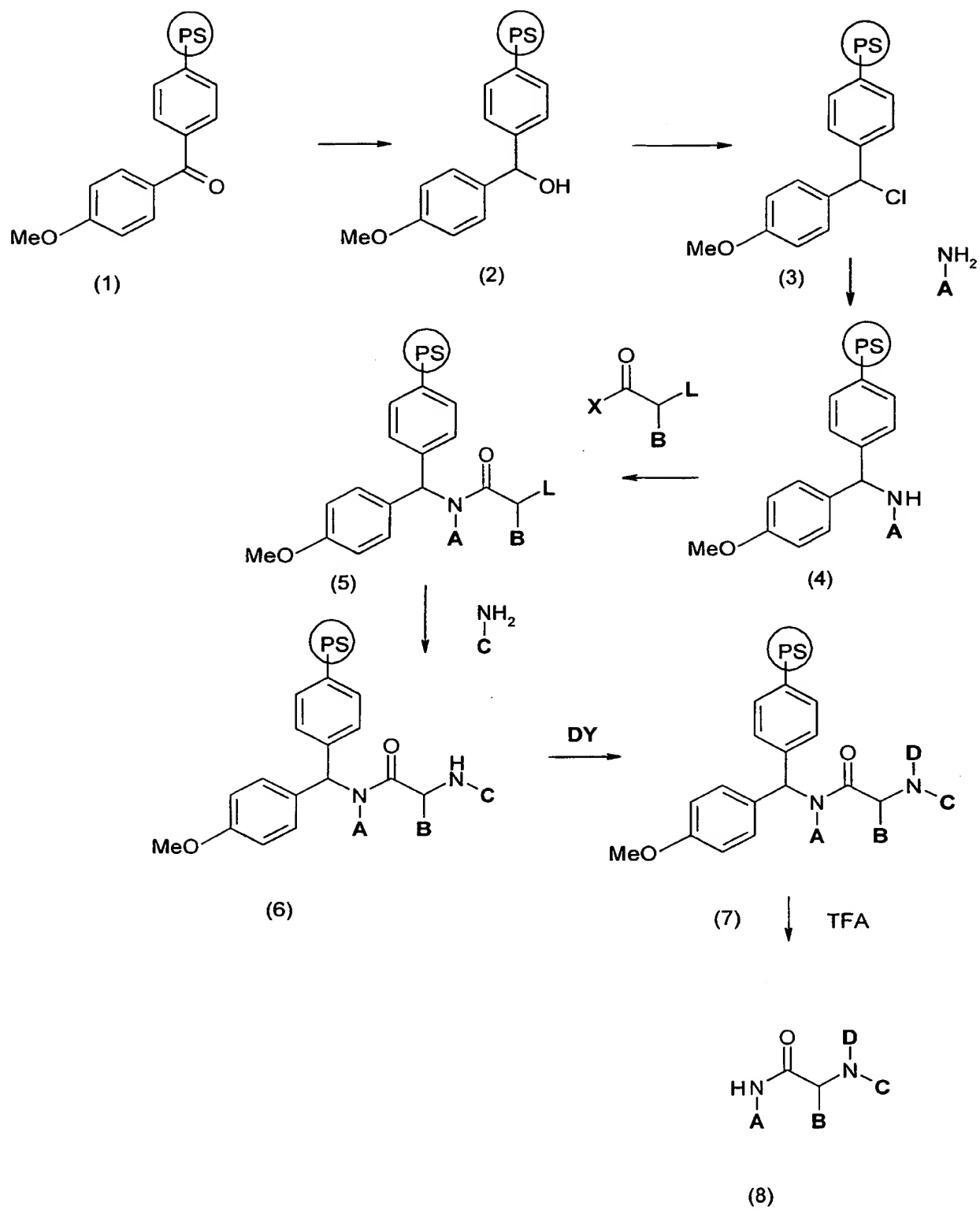
35 Preparation of N-benzoyl 2-thiophenylmethylamine from Poly[4'-methoxyphenyl-(2-thiophenylmethylamino)methyl]-4-styrene Polymer Composite

A piece of composite (0.25 g, approximately 4 x 5 cm) from Example 6 was placed in a vial and DCM (5 ml) added. Benzoyl chloride (0.19 ml) and pyridine (0.13 ml) were added and the vial placed on an rolling agitator for 3 hours. The composite was

removed from the solution and washed with DCM (x3), a mixture of 3:1 THF/1M aqueous HCl (x2), 3:1 THF/water (x2), THF, and finally DCM. A cleavage solution of 90:9:1 of DCM/ trifluoroacetic acid/water (5 ml) was added to the composite and the reaction was shaken gently for 30 min. The composite was rinsed with a further portion of the
5 cleavage solution and the combined solutions were concentrated on a rotovap. Toluene was added to the residue which was concentrated on a rotovap before being placed under vacuum for 20 min. This gave the title compound as cream solid (12 mg); NMR δ 4.81(2H,d); 6.5(1H,brs); 7.0(2H,m); 7.23(1H,d); 7.3-7.6(3H,m); 7.78(2H,m) ppm. Mass Spectrum EI 217, CI 218.

10 Example 8

This example illustrates the extension of the processes of Examples 3 to 7 to the synthesis of a chemical library using a polymer composite according to the invention. The process is illustrated in Scheme I below:



The polystyrene polymer composite of Example 2 was functionalised by treating the polystyrene with a benzoyl chloride, preferably 4-anisoyl chloride, in the presence of a Lewis acid catalyst, for example iron (III) chloride, in a suitable solvent, for example dichloromethane, to give benzophenone (1) as described in Example 3. The benzophenone (1) was reduced with a suitable reducing agent, for example lithium borohydride, in a suitable solvent or mixture of solvents, e.g. THF, to give the benzhydryl product (2) as described in Example 4. Chlorination to give (3) was effected using acetyl chloride in a suitable solvent such as toluene and at a suitable temperature, e.g. 65°C, as described in Example 5. Alternatively the chlorination may be effected by treatment with hydrogen chloride or phosgene alternatively with triphenyl phosphine in hexachloroethane.

The first building block or diversity element was put in place by reaction of the chlorohydryl product (3) with an amine (NH_2A) to give (4) as described in Example 6.

The amine (4) may now be treated with a variety of reagents in order to build up the target or template.

In this case amine (4) was treated with an acid chloride (9) where X is chlorine, L is a leaving group such as chlorine or bromine and B is, for example, alkyl or aryl, to give (5). The leaving group L was then displaced by a nucleophile, such as an amine (NH_2C), to give (6). The substrate (6) was treated with a reagent DY, e.g. an acid chloride, isocyanate, isothiocyanate, sulphonyl chloride or an alkylating agent, to give the product (7). The product (7) was then cleaved from the solid phase by treatment with an acid, for example trifluoroacetic acid (TFA) in dichloromethane with water in the ratio of, for example 90:9:1 to yield the final product (8) a secondary amide. Each of the substrates (5, 6 and 7) may also be treated with an acid to liberate the intermediate products.

CLAIMS

1. A process for the production of a functionalised cross-linked non-(meth)acrylate polymer composite comprising polymerising a non-(meth)acrylate monomer,
5 oligomer or monomer/oligomer mixture, in a substantially planar inert porous non-cellulosic solid substrate under conditions whereby the non-(meth)acrylate monomer, oligomer or monomer/oligomer mixture is substantially unreactive towards the substrate.
- 10 2. A process according to claim 1, which comprises initiating polymerisation in the monomer, oligomer or monomer/oligomer mixture prior to its introduction onto the inert substrate.
- 15 3. A process according to claim 1 or 2, which comprises mixing an accelerator which will catalyse polymerisation at room temperature into the monomer, oligomer or monomer/oligomer mixture prior to its introduction onto the inert substrate.
4. A process according to any one of the preceding claims, wherein the inert porous, non-cellulosic solid substrate is a flat sheet material.
- 20 5. A process according to any one of the preceding claims, wherein the monomer, oligomer or monomer/oligomer mixture is pre-functionalised so as to render the resulting polymer suitable for solid phase chemical synthesis.
- 25 6. A process according to any one of the preceding claims, wherein the polymer is a substituted polystyrene.
7. A functionalised cross-linked polymer composite obtainable by a process according to any one of claims 1 to 6.
- 30 8. A polymer composite according to claim 7, wherein portions of the polymer composite comprising discrete reaction zones for chemical synthesis are labelled, such that at least part of the reaction history of an individual zone can be elucidated following said chemical synthesis.
- 35 9. The use of a polymer composite according to claim 7 or 8 as a solid support for chemical library synthesis.

10. A chemical library comprising a plurality of different chemical compounds bound to discrete portions of a polymer composite according to claim 7 or 8.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 98/03732

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K1/04 C08F8/00 C08L25/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K C08F C08L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	WO 90 02749 A (FORSKNINGSCENTER RISQ) 22 March 1990 cited in the application see page 7, line 11 - page 8, line 17 see page 10, line 28 - page 11, line 16 see page 16, line 18 - page 17, line 11 see page 17, line 15 - page 19, line 28; claims 1-65 ---	1-10
Y	EP 0 710 666 A (NISSHINBO INDUSTRIES, INC.) 8 May 1996 see page 3, line 39 - line 53; claims 1-10 ---	1-10
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Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International Application No.

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